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EXAMINER	
SKIBINSKY, ANNA	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WENDELL LIM, JOHN DUEBER, and BRIAN YEH

Appeal 2008-3676
Application 10/613,380
Technology Center 1600

Decided[1]: March 18, 2009

Before DONALD E. ADAMS, DEMETRA J. MILLS, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1, 2, 6, and 8. The Examiner has objected to pending claim 14.[2] Pending "[c]laims 3-5, 7, 9-

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

[2] This objection is a petitionable matter, and therefore is not properly before us on appeal. Accordingly, we do not consider this objection as part of our deliberations.

11, and 15-22 are withdrawn from consideration" (App. Br. 2). We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to an autoregulated fusion protein. Claim 1 is illustrative:

1. An autoregulated fusion protein comprising an output domain and a plurality of input domains, wherein at least one of the input domains is heterologous to the output domain, and the input domains interact with each other to allosterically and external ligand-dependently regulate the output domain.

The Examiner relies on the following prior art references to show unpatentability:

Eliana De Bernardez Clark, "Protein refolding for industrial processes," 12 *Current Opinion in Biotechnology* 202-207 (2001).

Jennifer L. Seffernick et al., "Melamine Deaminase and Atrazine Chlorohydrolase: 98 Percent Identical but Functionally Different," 183(8) *Journal of Bacteriology* 2405-2410 (Apr. 2001).

David Baker et al., "Protein Structure Prediction and Structural Genomics," 294 *Science* 93-96 (Oct. 2001).

Jean-Denis Pédelacq et al., "Engineering soluble proteins for structural genomics," 20 *Nature Biotechnology* 927-932 (Sept. 2002).

John E. Dueber et al., "Reprogramming Control of an Allosteric Signaling Switch Through Modular Recombination," 301 *Science* 1904-1908 (Sept. 2003).

Se-Ho Kim, "Expression and purification of recombinant immunotoxin-a fusion protein stabilized a single-chain fv (scFv) in denaturing condition," 27 *Protein Expression and Purification* 85-89 (2003).

Fiona Cunningham et al., "Optimizing synthesis and expression of transmembrane peptides and proteins," 41 *Methods* 370-380 (2007).

The rejection presented by the Examiner is as follows:

Claims 1, 2, 6, and 8 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

We affirm.

ISSUE

Do Appellants provide an enabling description of their claimed invention?

FINDINGS OF FACT

FF 1. Appellants disclose that their "invention is in the field of creating synthetic logic gates with fusion proteins" (Spec. 1: 12). In this regard, Appellants disclose that

> We have developed a general strategy for introducing novel regulatory control over protein activities. We covalently fuse an unregulated, typically catalytic "output" domain to one or more "input" protein interaction domains and their ligands in a manner such that the intramolecular interactions act to conformationally or sterically inhibit the function of the output domain, a state referred to as "autoinhibition"

(Spec. 2: 7-11.)

FF 2. Appellants disclose that "[u]nder basal conditions the output of the output domain is down-regulated; however, in the presence of one or more

external stimuli, such as competitive ligands or covalent modifications that disrupt the autoinhibitory interactions, the output domain is de-repressed and the output activity is up-regulated" (Spec. 2: 11-14).

FF 3. Appellants disclose that "[t]he activity of the output domain is user discretionary" (Spec. 4: 30-31). In addition, Appellants disclose that "[t]he output domain is discretionary according to the intended use, and essentially any output domain providing a desired activity or binding affinity may be employed, so long as output activity can be regulated by ligand-dependent interaction of the input domains" (Spec. 6: 13-15).

FF 4. Appellants disclose that "output domains may be conveniently selected from *the enormous variety* of natural, modular catalytic domains or well-known, semi-synthetic engineered or derivitized modular catalytic domains" (Spec. 6: 20-22 (emphasis added)).

FF 5. Appellants disclose that "[o]utput domain functional compatibility with the fusion proteins is readily confirmed in activity screens" (Spec. 6: 16-17).

FF 6. Appellants list a number of "[v]alidated output domains" in Table 1 of the Specification (Spec. 6: 25 - 7: 7).

FF 7. Appellants disclose that "[t]he selection of input domains is user discretionary, so long as the selected domains interact to provide the requisite ligand-dependent gating of the output domain" (Spec. 7: 18-19).

FF 8. Appellants disclose that "[m]ultiple input domains can cooperatively regulate the fusion protein in a wide variety of functionalities, including as an OR-gate, an AND-gate, and an AND-NOT-gate" (Spec. 5: 8-9). Appellants disclose that "[t]he switches are readily designed or screened

such that the external ligand activation up-regulates, down-regulates, or otherwise alters output activity" (Spec. 7: 8-10).

FF 9. Appellants disclose that "[i]nput domain functional compatibility (demonstrating gating behavior) with the fusion proteins is readily confirmed in activity screens" (Spec. 7: 19-21).

FF 10. Appellants disclose that "[a] wide variety of input [domains] may be obtained, depending on the ultimate user application" (Spec. 7: 21-22).

FF 11. Appellants disclose that "[t]he input domain interaction can be provided by homo- or hetero-dimerization, by specific pair binding, by higher order complex formation, by enzyme-substrate catalysis (e.g. phosphorylation, glycosylation, prenylation, acylation, lipid modification, etc.)" (Spec. 7: 27-30).

FF 12. Appellants disclose that in order "[t]o promote their interactions, one or more of the input domains may be coupled to the fusion protein through a linker or spacer peptide" (Spec. 7: 31-33). However, Appellants also disclose that "[l]inker sequence and length are user-discretionary, though the linkers should not interfere with the output domain when the switch is in the active state (e.g. de-repressed) which is readily confirmed empirically" (Spec. 7: 31 - 8: 2). Nevertheless, Appellants disclose that "[l]inker length can . . . affect switch behavior" (Spec. 25: 17).

FF 13. Appellants disclose that "suitable input domains may be derived from[, inter alia, the] vast public databases of known interacting proteins" (Spec. 8: 8-9).

FF 14. Appellants disclose "[e]xemplary input domain pairs" in Table 2 of the Specification (Spec. 8: 22 - 18: 23).

FF 15. Appellants disclose that "[a] *wide variety* of external ligands may be used to activate the switches by interacting with one or more of the input domains" (Spec. 18: 24-25 (emphasis added)).

FF 16. Appellants disclose the construction of a N-WASP-based switch (Spec. 21: 22 - 23: 3).

FF 17. Appellants disclose that in order to produce a multi-input switch, they started with their N-WASP-based switch, "generated a library of constructs in which we combinatorially varied switch design parameters including domain type, domain-ligand affinity, linker length, and domain architecture" and then screened for activity (Spec. 23: 16-18; 24: 10).

FF 18. Appellants disclose that the result of their screen for a multi-input switch resulted in switches that "could be divided into diverse classes" ranging from switches that "showed little or no basal repression" and switches that "were extremely well-repressed, but could not be activated by these input concentrations" to switches that "showed gating behavior". Of the constructs that showed gating behavior, Appellants disclose that they obtained both two proteins exhibiting "OR-gate-like behavior" and five proteins exhibiting "AND-gate-like behavior, while the remaining constructs showed intermediate behavior" (Spec. 24: 17-29).

FF 19. In sum, Appellants disclose that "this relatively small library yielded a wide diversity of switch behaviors, including several with the targeted AND-gate behavior" (Spec. 24: 27-29).

FF 20. The Examiner finds that Appellants' Specification provides an enabling description of "an autoregulated fusion protein with an N-WASP output domain, PDZ and SH3 input domains (with the domains in this order in the sequence), wherein the input domains cooperatively regulate the

output domain as an AND-gate" (Ans. 4). The Examiner finds that Appellants' Specification "does not provide guidance for predictably making any [other] autoregulated protein" (*id.*).

FF 21. The Examiner finds that "[t]here is insufficient guidance for engineering *any* autoregulated fusion protein that will [ ]allosterically and external, ligand-dependently regulate the output domain" (*id.*). In this regard, the Examiner finds that Appellants' Specification "does not provide detailed guidance on how to achieve the synthesis of such an autoregulated protein using all of the domains listed in the [S]pecification" (Ans. 5).

FF 22. The Examiner finds that "[t]he prior art does not discuss autoregulated fusion proteins comprising output domains and input domains where the input domains interact with each other to allosterical[l]y and external ligand-dependently regulate the output domain" (Ans. 9).

FF 23. The Examiner relies on Cunningham, Kim, Clark, Pedelacq, Baker, and Seffernick to teach the state of the prior art (Ans. 6-8).

PRINCIPLES OF LAW

Enablement is a question of law, based on underlying findings of fact.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *In re Forman*, [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (footnote omitted).

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.

In re Wright, 999 F.2d 1557, 1561-62, (Fed. Cir. 1993).

"[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Wright*, 999 F.2d at 1561 (emphasis added), quoted in *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23 (Fed. Cir. 1991), quoted in *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999).

ANALYSIS

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative.

The nature of the invention and the breadth of the claimed invention:

The invention involves the use of protein engineering methods to covalently fuse an unregulated "output" domain to a plurality of "input" protein interaction domains to produce what Appellants refer to as "synthetic logic gates" or protein switches (FF 1).

Claim 1 is drawn to an autoregulated fusion protein. The claimed fusion protein comprises the following domains:

1. an output domain and

2 a plurality of input domains.

Thus, claim 1 is open to include any "output domain" fused, directly or through a linker, to any of a number of "input domains" (FF 3, 4, 7, 10, and 12).

Claim 1 places only two limitations on these domains. Specifically, claim 1 requires that:

a. at least one of the input domains is heterologous to the output domain, and

b. the input domains interact with each other to allosterically and external ligand-dependently regulate the output domain.

Therefore, the scope of the claimed invention is extremely broad.

The relative skill of those in the art:

The level of skill in the protein engineering art is high and involves the recombinant analysis of proteins, including fusion proteins (FF 23).

The predictability or unpredictability of the art:

The evidence relied upon by the Examiner confirms that the protein engineering art is unpredictable (FF 23).

The state of the prior art:

The Examiner finds that "[t]he prior art does not discuss autoregulated fusion proteins comprising output domains and input domains where the

input domains interact with each other to allosterical[l]y and external ligand-dependently regulate the output domain" (FF 22).

The presence or absence of working examples:

Appellants provide a working example of "an autoregulated fusion protein with an N-WASP output domain, PDZ and SH3 input domains (with the domains in this order in the sequence), wherein the input domains cooperatively regulate the output domain as an AND-gate" (*see e.g.,* FF 20).

Appellants also exemplify a combinatorial library based off of this N-WASP construct which resulted in the production of fusion proteins with a variety of activities (FF 17-19).

The amount of direction or guidance presented:

Appellants' Specification discloses that essentially any two or more input domain can be coupled, with or without a linker, to essentially any output domain to produce a desired autoregulated fusion protein (FF 4, 6, 7, and 10-14; *see also* App. Br. 3). In this regard, Appellants' disclose that one can screen the input and output domains to determine if they are functionally compatible with the autoregulated fusion protein one intends to make (FF 5 and 9; *see also* App. Br. 3-4). Stated differently, a person of ordinary skill in the art is left to figure out if any particular set of two or more input domains and output domain are compatible with each other.

According to Appellants' Specification, in order to obtain a specific fusion protein within the scope of the claimed invention one must first screen input and output domains to determine if they are compatible with each other to produce a first fusion protein containing a single input and

output domain (*id.*). Then, apparently, once a person of ordinary skill in the art obtains this first fusion protein comprising a compatible single input and single output; one would then be required to prepare a combinatorial library based on this first fusion protein containing fusion proteins that comprise a "plurality" of input domains and then screen this combinatorial library for the activity one hopes to obtain (FF 16-19).

Simply stated, Appellants' Specification provides no guidance on how a person of ordinary skill in the art would predictably produce a desired fusion protein within the scope of the claimed invention that has a desired activity, e.g., an AND-NOT-gate based on a person of ordinary skill in the arts preference for or choice of a particular set of input and output domains that have a particular ligand binding affinity and activity (*see e.g.,* FF 8).

The quantity of experimentation necessary:

Based on the foregoing discussion, an extremely large amount of experimentation would be required to obtain a fusion protein comprising a particular set of input and output domains that have a particular ligand binding affinity and activity.

At best, Appellants have provided what appears to be an interesting avenue of further research. They, may have even paved the way for further research (*see e.g.*, App. Br. 6). What they have not done is provide an enabling description of the claimed invention that would allow a person of ordinary skill in the art to practice the claimed invention without undue experimentation.

Other than the recommendation that one do the screens and figure it out for yourself, Appellants have provided no guidance on how to

successfully select the appropriate plurality of input domains that can be fused, with or without a linker, to an output domain to successfully obtain a fusion protein with the properties one would desire, e.g., an AND-NOT-gate based on a particular set of input and output domains that have a particular ligand binding affinity and activity.

We recognize Appellants' reliance on the Bourne Declaration (App. Br. 7). The Bourne Declaration, however, fails to establish how a person of ordinary skill in the art will fill in the foregoing gaps in Appellants' disclosure without undue experimentation. In this regard, we recognize the Bourne Declaration's citation of Adler[3] to suggest that "[t]hose skilled in the art have recognized that the invention is not limited to a single embodiment, but that Applicants' teachings '…pave the way for creating new signal-response elements by protein design[']" (Bourne Dec. 3). However, we find that providing an interesting avenue for further research (e.g., paving the way) is not the same as providing a disclosure that enables a person of ordinary skill in the art to practice the claimed invention without undue experimentation.

In sum, for the foregoing reasons, and absent persuasive evidence to the contrary, we are not persuaded by the Bourne Declaration.

CONCLUSION OF LAW

Appellants failed to provide an enabling description of their claimed invention.

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[3] Adler et al. *2003: Signaling Breakthroughs of the Year*, Science's STKE www.stke.org/egi/content/full/sigtrans;2004/214eg1 (2004).

The rejection of claim 1 under the enablement provision of 35 U.S.C. § 112, first paragraph is affirmed. Claims 2, 6, and 8 fall with claim 1.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc:

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